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Golgi trafficking defects in postnatal microcephaly: the evidence for "Golgipathies"

Sandrine Passemard[1,2], Franck Perez[3], Emilie Colin-Lemesre[1,3], Sowmyalakshmi Rasika[1], Pierre Gressens[1,4], Vincent El Ghouzzi[1*]

1. PROTECT, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France
2. AP HP, Hôpital Robert Debré, Service de Génétique Clinique, Paris, France
3. Institut Curie, PSL Research University, CNRS, UMR144, Paris, France
4. Centre for the Developing Brain, Division of Imaging Sciences and Biomedical Engineering, King's College London, King's Health Partners, St. Thomas' Hospital, London, United Kingdom

***Corresponding author:**

Vincent El Ghouzzi

Address: Inserm U1141, Hôpital Robert-Debré, 48 Boulevard Sérurier, F-75019, Paris, France.

E-mail: vincent.elghouzzi@inserm.fr

Phone: +331 40031973, Fax: +331 40031995

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Abstract

The Golgi apparatus plays a central role in cell homeostasis, not only in processing and maturing newly synthesized proteins and lipids but also in orchestrating their sorting, packing, routing and recycling on the way to their final destination. These multiple secretory pathways require a complex ballet of vesicular and tubular carriers that continuously bud off from donor membranes and fuse to acceptor membranes. Membrane trafficking is particularly prominent in axons, where cargo molecules have a long way to travel before they reach the synapse, and in oligodendrocytes, which require an immense increase in membrane surface in order to sheathe axons in myelin. Interestingly, in recent years, genes encoding Golgi-associated proteins with a role in membrane trafficking have been found to be defective in an increasing number of inherited disorders whose clinical manifestations include postnatal-onset microcephaly (POM), white matter defects and intellectual disability. Several of these genes encode RAB GTPases, RAB-effectors or RAB-regulating proteins, linking POM and intellectual disability to RAB-dependent Golgi trafficking pathways and suggesting that their regulation is critical to postnatal brain maturation and function. Here, we review the key roles of the Golgi apparatus in post-mitotic neurons and the oligodendrocytes that myelinate them, and provide an overview of these Golgi-associated POM-causing genes, their function in Golgi organization and trafficking and the likely mechanisms that may link dysfunctions in RAB-dependent regulatory pathways with POM.

Contents

1. Introduction

Microcephaly affects about 2% of the population worldwide and represents the most frequent neurological sign encountered in developmental brain disorders. It is characterized by a small brain size, indirectly diagnosed by an occipito-frontal or head circumference (OFC) smaller than the age- and gender-adjusted mean by more than 2 standard deviations (SD) at birth and/or 3 SD as measured at 6 months of age or later; it is frequently associated with intellectual disability of variable severity. Among the many kinds of microcephaly, genetic forms have yielded essential information as to how the human brain develops during embryonic/fetal and postnatal periods. While primary microcephaly is defined by a congenital failure of brain growth detectable before birth, secondary (or postnatal-onset) microcephaly (POM) is characterized by normal brain size at birth and the subsequent deceleration of brain growth, and in particular the white matter, during infancy and/or childhood. In the past 15 years, considerable efforts have led to the identification of genes and pathways whose deficiency causes hereditary primary microcephaly, also known as MCPH. The vast majority of MCPH genes (17 identified to date, see updated review by (Alcantara and O'Driscoll, 2014)) play a role in the regulation of cell division and/or centrosome function in neural progenitors, and a large number of functional studies now converge on common mechanisms that affect the mode and/or extent of cortical progenitor division and their subsequent survival and differentiation during the development of the neocortex. In contrast, POM or acquired microcephaly, which often appears to be only one of many clinical signs in complex and divergent syndromes, is not always considered a disorder on its own. As such, it is underdiagnosed and underinvestigated, and the cellular mechanisms leading to it are poorly understood.

The timing of POM suggests that these cellular mechanisms presumably involve processes and pathways that occur later during development than neuronal progenitor division, the major process implicated in primary microcephaly. Indeed, several principally postnatal

mechanisms that could lead to POM, such as defective gliogenesis or myelination, the impairment of neuronal maturation or synaptic pruning, the arrest of normal development or degenerative processes, have received much attention from the scientific community in recent years. One candidate process worth noting is membrane trafficking and secretion through the Golgi apparatus. Indeed, several recent studies have implicated Golgi-associated proteins in genetic disorders that include POM among their characteristics, suggesting that the regulation of Golgi trafficking and secretory functions are critical to postnatal brain maturation. Intriguingly, a number of these POM-causing genes encode either RAB proteins - members of the RAS superfamily of small GTPases which play a central role in membrane trafficking including Golgi organization, vesicle formation, transport and fusion – or RAB-associated or RAB-tethering factors whose fast and reversible recruitment facilitates such trafficking. Interestingly, all these POM-causing genes are associated with the defective development of white matter, which consists principally of the axons of neurons and the myelinating oligodendrocytes that ensheathe them, highlighting the link between the heavy membrane trafficking and secretory activity of these two interdependent cellular components and postnatal brain development.

In this review, we describe the key roles played by the Golgi apparatus in post-mitotic neurons and oligodendrocytes, describe recently identified POM-causing genes associated with the Golgi apparatus, and discuss the intriguing fact that many of these appear to encode RAB proteins or their molecular partners. In light of their role in Golgi organization and trafficking and the mechanistic links between RAB proteins, white matter defects and the development of POM, we propose a new term for these disorders based on their similar pathophysiology: "Golgipathies"/"Golgipathic microcephalies".

2. The Golgi apparatus in post-mitotic neurons and oligodendrocytes

The Golgi apparatus is a multifunctional organelle essential to ensure differentiated cellular functions as well as to maintain cell homeostasis. In mammalian cells, about one-third of newly synthesized proteins are destined to be secreted following the conventional secretory pathway. The Golgi apparatus is primarily involved in the processing of secretory proteins and lipids as they transit through it, effecting posttranslational modifications such as glycosylation, sulfation and proteolytic cleavage. The Golgi apparatus also acts in the sorting, packing, routing and recycling of these cargo molecules for their final destination. Depending on the cell type and stage of development, Golgi-dependent trafficking routes and secretory cargos have become diversified to fulfill specific secretory functions (Boncompain and Perez, 2013a). This is especially true of two cell types that are heavily affected in POM: post-mitotic projection neurons and the oligodendrocytes that enwrap their axons in myelin, with several studies showing that the Golgi apparatus plays a key role in the dynamic trafficking specific to the axonal and dendritic compartments of these neurons, as well as the extensive plasma membrane extensions of oligodendrocytes required for myelin formation. Besides its involvement in protein and lipid trafficking/processing in these two cell types, the Golgi apparatus is also involved in the determination and maintenance of neuronal polarity, as well as in autophagy, another process essential both for brain development and homeostasis of mature neural cells.

2.1 Role of the Golgi apparatus in neuronal polarity

In mammalian cells, the Golgi apparatus is a ribbon-shaped organelle made up of flattened cisternae organized into polarized stacks, flanked on either side by fenestrated tubular reticular membranes called the *cis*-Golgi network (CGN) and the *trans*-Golgi network (TGN) (Nakamura *et al.*, 2012; Papanikou and Glick, 2014). In most cells, the Golgi apparatus is positioned near or around the centrosome, with which it is dynamically associated through the action of cytoplasmic dynein motor proteins and Golgi anchor proteins (Yadav and Linstedt, 2011). In developing neurons, centrosomes, the Golgi apparatus and endosomes cluster

together at one pole of the cell body before neurites form, and play a key role in axon specification (Caceres, 2007). Although the existence of a direct correlation between Golgi/centrosome positioning and the area where the future axon will form has remained controversial (de Anda *et al.*, 2005; Distel *et al.*, 2010; Horton *et al.*, 2005; Lowenstein *et al.*, 1994; Zmuda and Rivas, 1998), this asymmetric pericentrosomal confinement of the Golgi apparatus likely leads to a local concentration of neuronal growth potential both in terms of cytoskeletal infrastructure and of newly synthesized proteins, two components essential for the elongation of the axon. Axonal outgrowth also requires a huge expansion of the plasma membrane surface (Horton and Ehlers, 2003), which is achieved by the progressive integration of Golgi-derived vesicles. Such vesicles have been shown to accumulate and polarize before axonogenesis in cultured hippocampal neurons (Bradke and Dotti, 1997). In line with this mechanism, brefeldin A treatment, which disassembles the Golgi apparatus, results in the selective inhibition of axonal growth (Jareb and Banker, 1997). Similarly, the genetic invalidation of certain Golgi-related proteins leads to altered neuronal polarity and death and/or dysfunction. For instance, in mice in which the expression of the golgin GM130 is invalidated by shRNA treatment or genetically knocked out, the polarity of the Golgi apparatus is altered, leading to altered dendritic polarization in granule cells of the hippocampus (Huang *et al.*, 2014), as well as altered ER-to-Golgi transport, inducing the atrophy and death of Purkinje cells of the cerebellum, and consequently, ataxia (Liu *et al.*, 2017). The loss of expression of two other golgins, Golgin-160 and GMAP210, which disrupt pericentrosomal Golgi positioning without affecting either the microtubule network or general secretion, also strongly affects cell polarity in vitro (Yadav *et al.*, 2009). However, the effect of GMAP120 deletion on Golgi structure or function might depend on the cellular subtype being examined (Smits *et al.*, 2010).

In addition to its involvement in neuronal development, the Golgi apparatus is required for the maintenance of axodendritic polarity throughout the lifespan of mature post-mitotic

neurons. These highly specialized cells possess specific architectural features that make the secretory pathway central to their structural maintenance, dynamics and function. In particular, their strongly polarized axons and dendrites are characterized by morphologically and functionally distinct components and pathways. This necessitates the asymmetric transport of membranes and the continuous targeting of distinct repertoires of cargo proteins and lipids to these distinct subcellular compartments. Mature neurons also often develop extensive dendritic branching accompanied by a huge increase in membrane surface area (Ye *et al.*, 2006). In addition, the long axons possessed by some neurons pose a perennial challenge to the movement of proteins, lipids, vesicles and organelles between cell bodies and synaptic sites. Although the mechanisms through which this differential targeting is specifically achieved and regulated are complex and only partially understood, a number of key findings show that the Golgi apparatus lies at the core of processes that elicit distinct secretory features in the axons and dendrites of post-mitotic neurons, thereby maintaining neuronal polarity.

2.1.1 Distribution of microtubules in neurons and their relationship to the Golgi apparatus

Microtubules, which themselves are polarized and serve as rails for active vesicular cargo transport driven by molecular motors, are asymmetrically distributed in axons and dendrites. While axons usually display long, uniformly oriented microtubules with their minus ends towards the soma and the plus ends facing outwards, proximal dendrites contain shorter microtubules oriented in both directions (Baas, 1999) (Figure 1A). In dendrites, the minus-end-out microtubules are generally more stable (Yau *et al.*, 2016), which contributes to generating directionality. This implies a difference in the organization of molecular motors involved in trafficking in the two compartments. For example, dynein, which moves along microtubules towards their minus end, drives retrograde transport in axons but bidirectional transport in dendrites, while kinesin motors seem to predominantly drive anterograde transport in axons

(Kapitein *et al.*, 2010). Interestingly, the Golgi apparatus not only sorts and provides the various cargos to be conveyed to specific destinations but also acts as a microtubule-organizing center (MTOC), independently of the centrosome (Chabin-Brion *et al.*, 2001; Zhu and Kaverina, 2013), and itself generates a distinct population of microtubules called Golgi-derived microtubules. During the development of rodent hippocampal neurons, the centrosome actually loses its function as a MTOC, and it is microtubules of non-centrosomal origin that enable axon extension and serve as rails for directional post-Golgi trafficking (Stiess *et al.*, 2010). Similarly, microtubule organization is independent of the centrosome in developing and mature Drosophila neurons (Nguyen *et al.*, 2011), and the Golgi apparatus has been proposed as a possible source of dendritic microtubules (Ori-McKenney *et al.*, 2012), a process promoted by the golgin GM130 (Zhou *et al.*, 2014). Interestingly, directional trafficking defects have been observed in human RPE1 cells lacking Golgi-derived microtubules, suggesting that the latter are essential for post-Golgi transport (Miller *et al.*, 2009; Vinogradova *et al.*, 2012). Thus, while further evidence is still required to confirm this possibility, the Golgi apparatus might also be directly involved in the maintenance of neuronal polarity in postmitotic neurons through its role as a MTOC.

2.1.2 *Specificity of Golgi-derived carriers*

The differential distribution of cargo proteins and lipids between dendrites and axons is largely due to specific and reciprocal interactions between cargos, their carriers and molecular motors. This occurs through the docking of motor proteins onto their specific cargos either directly or via adaptor molecules, including scaffolding proteins, receptors and Rab GTPases that regulate neuronal transport (Franker and Hoogenraad, 2013; Maeder *et al.*, 2014; Schlager and Hoogenraad, 2009). Interestingly, the identity of the various carriers is in large part conferred by the specific cargos they carry. The sorting of axonal and dendritic cargo proteins and lipids occurs in the TGN, where they are physically segregated into specific clusters that

define specific dynamic TGN subdomains, ultimately leading to vesicle budding. This physical segregation of cargos appears to rely on both the intrinsic affinity of different cargos for specific lipid microenvironments provided by the TGN (Brugger *et al.*, 2000; Klemm *et al.*, 2009; Orci *et al.*, 1987; Paladino *et al.*, 2004; Schuck and Simons, 2004); reviewed in (Anitei and Hoflack, 2011; De Matteis and Luini, 2008; Guo *et al.*, 2014; Lingwood and Simons, 2010; Surma *et al.*, 2012), and the presence of sorting signals on cargo molecules that target them to TGN-specific adaptors such as small ADP ribosylation factors, Rab and Rho GTPases, and Golgi-localized tethering factors (De Matteis and Luini, 2008). In other words, the selective targeting of cargos that contribute to the axodendritic polarity of neurons starts as soon as the cargos reach the TGN (Guo *et al.*, 2014).

2.1.3. *Golgi outposts in dendrites*

In addition to the somatic Golgi apparatus, the Golgi complex forms smaller satellite structures called Golgi outposts that are found in about 20% of the dendrites of mature neurons (Gardiol *et al.*, 1999; Horton *et al.*, 2005; Pierce *et al.*, 2001) (Figure 1A). Several studies have provided evidence that these Golgi outposts lack continuity with the somatic Golgi apparatus and are functionally independent. Golgi outposts ensure the post-translational modifications, trafficking and sorting of locally synthesized proteins (Horton *et al.*, 2005; Jeyifous *et al.*, 2009; Torre and Steward, 1996; Ye *et al.*, 2007), as well as local microtubule nucleation (Ori-McKenney *et al.*, 2012), thereby playing a major role both in shaping dendritic arbor morphology and in serving as platforms for the local delivery of postsynaptic molecules such as synaptic receptors. In line with this role, and consistent with the recent demonstration that Golgi outposts destined for the major dendrite are generated by a sequential process that involves the polarized deployment and fission of tubules derived from the somatic Golgi (Quassollo *et al.*, 2015), markers of *cis*, *medial* and *trans* Golgi compartments have all been detected in dendrites (Horton *et al.*, 2005; Pierce *et al.*, 2001). Reinforcing the role of the Golgi

apparatus in the functional specialization of dendrites, a recent study by Mikhaylova provides evidence for a Golgi-related satellite microsecretory system in dendrites that is even more widespread than Golgi outposts and would permit the autonomous local control of membrane protein synthesis and processing within dendrites (Mikhaylova *et al.*, 2016).

2.1.4. *Golgi components in axons*

Besides the well-described transport mechanisms that direct cargos to axons through molecular motors and microtubules, and ensure their activity, function and plasticity (Hirokawa and Takemura, 2005), growing evidence suggests that a number of axonal proteins are locally synthesized from mRNAs and ribosomes present in axons and presynaptic elements (Sotelo-Silveira *et al.*, 2006; Yoo *et al.*, 2010). The existence of such decentralized protein synthesis could allow axons to meet local demands in a fast and energy-efficient manner, as is the case with dendrites (Donnelly *et al.*, 2010; Holt and Bullock, 2009; Jung *et al.*, 2012). However, whether this process also involves the presence of Golgi outpost-like structures in axons is a matter of debate. The presence of early secretory components, including markers of the ER, the ER-Golgi intermediate compartment (ERGIC), Golgi apparatus and TGN, has been observed by some authors in the distal axoplasm of rat peripheral axons (Gonzalez *et al.*, 2016; Merianda *et al.*, 2009), raising the possibility that these components self-organize into small functional organelles in situ. Although rough ER and Golgi stacks have not so far been observed in axons at the ultrastructural level (reviewed in (Ramirez and Couve, 2011)), the occurrence of local protein synthesis suggests that protein processing and secretory needs could also be met locally, rendering axons at least partially independent of the somatic early secretory pathway and facilitating, for example, fast membrane receptor recycling in response to local conditions.

2.2 Role of the Golgi apparatus in myelination

Most neurons are characterized by a myelin sheath that enwraps their axons and is responsible for the whitish appearance of the white matter of the brain. In the central nervous system (CNS), the myelin sheath is a multilamellar structure consisting of the plasma membrane extensions of oligodendrocytes, with a single mature oligodendrocyte ensheathing several axons. These lipid-rich processes are extremely long and packed in tight spirals around axons, forming a dense sheath to protect and insulate them and thus ensure the high-speed propagation of electrical impulses. A stereological study carried out in a 20 year-old man has revealed a total myelinated fiber length of 170,000 kilometers (Marner *et al.*, 2003); the dimensions of the oligodendrocytic processes required to ensheathe these fibers must therefore be many times greater. The biogenesis and maintenance of this vast quantity of myelin implies an intensive and sustained supply of membrane proteins and lipids. In oligodendrocytes, as in neurons, this is achieved both through the local synthesis of myelin components close to the site of their assembly, and through intensive vesicle trafficking mechanisms involving the traditional ER-Golgi-TGN pathway (Kramer *et al.*, 2001). For example, myelin basic protein (MBP), which represents approximately 30 percent of myelin proteins and plays a major role in myelin compaction (Privat *et al.*, 1979) and composition by regulating its protein to lipid ratio (Aggarwal *et al.*, 2011), is synthesized on the spot by the local translation of MBP mRNAs (Colman *et al.*, 1982), following their packing in a translationally repressed state (Bauer *et al.*, 2012; Kosturko *et al.*, 2006) into large ribonucleoprotein complexes called RNA transport granules (Muller *et al.*, 2013), and their transport along microtubules into the myelin compartment (Ainger *et al.*, 1993; Carson *et al.*, 1997). In contrast, myelin-specific lipids and other major myelin proteins, such as the proteolipid protein PLP, are synthesized in the soma of mature oligodendrocytes and pass through the Golgi where they are processed and self-assemble with cholesterol and sphingolipids to form a type of preformed myelin modules called lipid-enriched liquid ordered membrane microdomains or lipid "rafts", which are transported through the secretory pathway (Gielen *et al.*, 2006; Simons *et al.*, 2000). However, the

technical complications inherent in observing nanoscale molecular organizations such as lipid microdomains in a reliable manner, i.e. without altering the object of the observation, has no doubt contributed to their being viewed by some authors as hypothetical rather than real structures for the present (see (Guo *et al.*, 2014)). Reciprocal communication between axons and oligodendrocytes is also required for the generation of the myelin sheath. In oligodendrocytes, such lipid microdomains, in addition to being components of myelin, behave as dynamic signaling modules in recruiting specific signaling proteins that integrate axon-derived soluble or membrane-bound signals to regulate myelination spatiotemporally (White and Kramer-Albers, 2014). The nodes of Ranvier, non-myelinated axon segments that are regularly placed along myelinated fibers, constitute privileged zones where molecular interchanges take place across the axonal membrane. In addition to specific cell adhesion molecules and cytoskeletal scaffold molecules that maintain the proper function and architecture of nodes (Susuki and Rasband, 2008), these nodes are also the sites of release of several axon-derived signaling molecules that have been shown to regulate the proliferation, differentiation and survival of oligodendrocytes, and control the onset and timing of myelin membrane growth (Simons and Trajkovic, 2006). For example, both the stability and the site-specific translation of MBP mRNA are promoted by the recruitment of the tyrosine kinase Fyn by oligodendrocytic lipid microdomains (White and Kramer-Albers, 2014), and its activation occurs in response to the binding of the axonal cell adhesion molecule L1 (White *et al.*, 2008). Interestingly, the myelin membrane protein TPO1, which has also been proposed to activate Fyn, is highly enriched both in the Golgi and in the Fyn-positive sheets of myelinating oligodendrocytes (Fukazawa *et al.*, 2006; Jain and Ganesh, 2016). Thus, the fine regulation of myelin formation and maintenance appear to depend on trafficking through the Golgi-dependent secretory pathway and microtubule network and signaling pathways in both oligodendrocytes and the neurons, and on their functional interactions at specific sites.

2.3 Role of the Golgi apparatus in autophagy

Autophagy or "self-eating" is an evolutionarily conserved catabolic process by which cytosolic contents are delivered to acidic lysosomes for degradation. It serves various purposes: the maintenance of cellular homeostasis by eliminating waste or toxic products and recycling cellular components and nutrients, especially during conditions of starvation, for protection against certain pathogens, as well as the facilitation of cellular remodeling. In contrast to the ubiquitin-proteasome system (which achieves the regulated degradation of individual ubiquitinated proteins), autophagy leads to the bulk degradation of whole organelles and large amounts of proteins. Of the three main types of autophagy – microautophagy, chaperone-mediated autophagy and macroautophagy – the last is the best studied, and is characterized by a newly formed "isolation membrane" or "phagophore" that grows to envelop the components to be degraded in a double-walled structure called the autophagosome, which subsequently fuses with the lysosome (for a broad review, see (Feng *et al.*, 2014; Mizushima and Komatsu, 2011)). For this reason, the term "autophagy" is often used to refer specifically to macroautophagy.

In the central nervous system with its specialized long-lived cells characterized by extensive membrane processes, in addition to its traditional role in maintaining cellular homeostasis (Hu *et al.*, 2015; Tooze and Schiavo, 2008), autophagy plays several other roles: the modulation of synaptic plasticity (Hernandez *et al.*, 2012), the maintenance of the pool of neural stem cells required for postnatal neurogenesis (Wang *et al.*, 2013), and finally, the normal development of the CNS, including neural progenitor proliferation, neuronal maturation, connectivity and myelination (Ban *et al.*, 2013; Hara *et al.*, 2006; Jang *et al.*, 2015; Kadir *et al.*, 2016; Kim *et al.*, 2016; Komatsu *et al.*, 2006; Liang *et al.*, 2010; Rangaraju *et al.*, 2010; Schwarz *et al.*, 2012; Smith *et al.*, 2013; Song *et al.*, 2008). As could be expected, defects in autophagy-related genes or dysfunctions of autophagy are reflected in a number of human neurological disorders (for review, see (Bockaert and Marin, 2015; Ebrahimi-Fakhari *et al.*, 2016; Yamamoto and Yue, 2014)).

Despite the fact that neurons were among the first cell types in which autophagosomes were observed (Dixon, 1967; Holtzman and Novikoff, 1965), most of the research into the mechanisms of autophagy has focused on other cell types and/or non-mammalian species. However, keeping in mind the highly conserved nature of this process, there is evidence from neuronal and non-neuronal models to show that, at the structural level, the nucleation and the elongation of the phagophore or isolation membrane might occur directly from the Golgi apparatus, although, depending on the cell type involved, the ER or the ERGIC have been proposed as alternative sources (Ge *et al.*, 2015; Lamb *et al.*, 2013). In alternative forms of autophagy (Atg5/Atg7-independent autophagy (Nishida *et al.*, 2009) or the recently discovered Golgi membrane-associated degradation (Yamaguchi *et al.*, 2016)), autophagosomes have been shown to bud directly from Golgi membranes. Using 3D electron tomography of cryopreserved brain tissue, Fernandez-Fernandez et al. have further described distinct engulfing Golgi structures as a potential site for the degradation of cytoplasmic contents in neurons (Fernandez-Fernandez *et al.*, 2017). At the functional level also, there are numerous links between Golgi-related proteins and autophagic processes. Beclin1 is involved in endosome-to-Golgi recycling but also plays a crucial early role in autophagosome formation (reviewed in (He and Levine, 2010)). The membrane-bound protein Atg9, normally involved in TGN-to-endosome transport, is found in vesicles that contribute to autophagosome formation (Longatti *et al.*, 2012), and the regulation of its trafficking plays a crucial role in the induction of autophagy pathways (Young *et al.*, 2006; Zhou *et al.*, 2017). The clathrin adaptor proteins AP1/2, involved in the clathrin coating of secretory vesicles and known to interact with Atg9, are also necessary for autophagosome formation at specific TGN domains (Guo *et al.*, 2012). UVRAG (UV radiation resistance-associated gene), which normally mediates Golgi-to-ER retrograde transport through the tethering of COPI-coated vesicles, is dissociated from the ER and used for the generation of autophagosomes during autophagy (He *et al.*, 2013). As discussed further below, several Golgi-associated RAB GTPases and their partners, involved in various stages of trafficking, also play

key roles in the formation of the autophagosome (Geng *et al.*, 2010; Itoh *et al.*, 2008; Longatti *et al.*, 2012; Oda *et al.*, 2016; Wen *et al.*, 2017) (see also **Table I**). In addition, SNAREs (soluble *N*-ethylmaleimide-sensitive fusion protein attachment proteins), small membrane-bound protein labels that help target vesicles to the Golgi apparatus, are also involved in the fusion of autophagosomes (reviewed in (Reggiori and Ungermann, 2017)). It appears thus that the membrane trafficking role of the Golgi apparatus and its role in autophagy are two sides of the same coin, with the molecular machinery involved in one function being requisitioned to serve the other according to cellular needs.

2.4 Role of Golgi-associated RAB proteins in the brain

RAB proteins are small GTPases that regulate the docking of cargo vesicles to their target compartments through specific interactions with tether, motor, and coat proteins at almost every step of membrane trafficking, and in both anterograde (secretory) and retrograde (endocytic and recycling) pathways. RAB proteins are considered to be molecular switches, cycling between an active form (bound to GTP) and an inactive form (bound to GDP). The switching between the two forms is regulated by guanine nucleotide exchange factors (GEFs), which promote the active GTP-bound state, and by GTPase-activating proteins (GAPs), which inactivate RABs by promoting hydrolysis of GTP to GDP (Barr and Lambright, 2010). Among the ~60 RAB GTPases identified so far in mammalian cells, 20 have been localized to the Golgi complex (Golgi-associated RABs) and 12 appear to be enriched in TGN membranes or to act between the TGN and recycling endosomes (**Table I**).

Golgi-associated RABs play critical roles in two tightly linked processes that jointly contribute to Golgi homeostasis - Golgi structural organization and membrane trafficking - as the maintenance of ribbon organization is essential for cargo proteins to be correctly modified and efficiently sorted (Liu and Storrie, 2012). An increasing number of studies show that each Golgi-associated RAB fulfils more than one function and can recruit a large number of

effectors in several different locations of the Golgi apparatus. Interestingly, many RABs, including several that are associated with the Golgi apparatus, appear to play a role in the morphogenesis or function of post-mitotic neurons, for example by promoting neurite elongation and/or enhancing dendritic growth and branching in neuronal cultures (Villarroel-Campos *et al.*, 2014). The involvement of some of these Golgi-associated RABs in the autophagic pathway could also be important for the maturation and maintenance of post-mitotic neurons and glia, as mentioned in the previous section (see also **Table I**). The flip side of this observation is that defects in some of these RABs or their effectors could be expected to lead to the abnormal morphogenesis or function of post-mitotic neurons, as seen for instance in disorders characterized by POM. This is precisely the case with RAB6, RAB1, RAB18, RAB33 and RAB39, which we will examine further below.

RAB6 is one of the most abundant and best-characterized Golgi-associated RABs (Goud, 2012). The RAB6 subfamily consists of 4 different isoforms, RAB6A, RAB6A', RAB6B and RAB6C. RAB6A and A', two isoforms encoded by the same gene, localize to the *medial* and *trans*-Golgi cisternae, cytoplasmic vesicles and TGN, and can recruit at least 15 different effectors through which they regulate Golgi vesicle biogenesis (Miserey-Lenkei *et al.*, 2010), vesicle tethering at the Golgi (Short *et al.*, 2002), intra-Golgi transport and retrograde transport from late endosomes via the Golgi to the ER (Heffernan and Simpson, 2014). Recent studies, however, suggest that the main function of RAB6 is to ensure the generation of post-Golgi carriers and their exocytosis (Grigoriev *et al.*, 2007; Grigoriev *et al.*, 2011). Nevertheless, in the context of microcephaly, the role of RAB6 in regulating retrograde transport and its functional interactions with other molecules involved in this process, RAB33B and the COG complex (Starr *et al.*, 2010; Sun *et al.*, 2007), are particularly intriguing (see next section). A second gene encodes the brain-specific isoform RAB6B, which is localized to structures similar to RAB6A/A', but is preferentially expressed in neuronal cells (Opdam *et al.*,

2000), where it also mediates retrograde membrane transport in neurites (Opdam *et al.*, 2000; Wanschers *et al.*, 2007); however, whether this transport also involves the Golgi-to-ER compartment has not been confirmed. Interestingly, RAB6A/A' and B are thought to play a key role in the regulation of neurite outgrowth during the early phase of neuronal differentiation, through the recruitment Bicaudal-D-related protein 1 and dynamic interactions with the kinesin motor Kif1C and the dynein/dynactin retrograde motor complex (Schlager *et al.*, 2010). RAB6C is encoded by a primate-specific intronless gene and is expressed in a limited number of human tissues (including brain). In contrast to other RAB6 proteins, RAB6C associates with the centrosome and is involved in cell cycle progression (Young *et al.*, 2010).

RAB1 is known to regulate anterograde membrane trafficking mediated by vesicles coated with the coatomer COPII between the ER and the Golgi, where its two isoforms RAB1A and RAB1B are predominantly expressed (Plutner *et al.*, 1991; Saraste *et al.*, 1995), but it is also present in lipid microdomains and in autophagosomes (Wang *et al.*, 2010; Zoppino *et al.*, 2010). As for RAB6, RAB1 can recruit many different effectors such as the golgins p115, GM130, GIANTIN, GRASP65 and GOLGIN-84, which act as tethers to help COPII-coated vesicles dock to *cis*-Golgi membranes (Alvarez *et al.*, 2001; Diao *et al.*, 2003; Moyer *et al.*, 2001; Satoh *et al.*, 2003; Weide *et al.*, 2001). Interestingly, Drosophila neurons lacking a functional *dar6* gene (the Drosophila RAB1 homolog) show reduced dendritic arborization (Ye *et al.*, 2007). Conversely, over-expression of RAB1 rescues defective vesicular trafficking in models of Parkinson disease with α-Synuclein-induced disruption of ER-to-Golgi transport (Cooper *et al.*, 2006). This suggests that RAB1 is critical to both neuronal differentiation and homeostasis.

RAB18, although less well studied, appears to have multiple roles as well, depending on cell type and differentiation stage, and a combination of effectors (Vazquez-Martinez and Malagon, 2011). In certain non-neuronal cells, e.g. adipocytes and hepatic stellate cells, RAB18 is associated with lipid droplets and functions in cell activation and lipid metabolism (Martin *et*

al., 2005; O'Mahony *et al.*, 2015; Ozeki *et al.*, 2005). In neuroendocrine cells, RAB18 cycles between the cytosol and the surface of a discrete population of secretory granules to reduce their transport, and thereby negatively modulates the secretory activity of the cells (Vazquez-Martinez *et al.*, 2007). In most cells, RAB18 is also present in the *cis*-Golgi and ER compartments (Dejgaard *et al.*, 2008) and is required to maintain the morphology of the perinuclear ER (Gerondopoulos *et al.*, 2014). There is good evidence that RAB18 can bind the ER-resident Dsl1 protein complex (Gillingham *et al.*, 2014), which tethers and fuses vesicles returning from the Golgi. This suggests that RAB18 may participate in the tethering of COPI-coated vesicles to the ER (Gillingham *et al.*, 2014; Schroter *et al.*, 2016). Interestingly, RAB18 is expressed in the developing mouse brain from E14.5, and its expression markedly increases around birth (Wu *et al.*, 2016). The depletion of RAB18 impairs the radial migration of neurons to the cortical plate *in vivo* and alters cortical neuron morphogenesis *in vitro* (Wu *et al.*, 2016), providing evidence that RAB18 is critical to neuronal positioning and maturation.

RAB33, another RAB of particular interest for brain maturation, exists as two closely related and conserved proteins encoded by distinct genes, *RAB33A* and *RAB33B*. Both are Golgi-associated proteins but RAB33A is found only in the brain, lymphocytes and melanocytes (Cheng *et al.*, 2006; Lee *et al.*, 2006; Zheng *et al.*, 1997), whereas RAB33B is ubiquitous (Zheng *et al.*, 1998). In the mouse brain, RAB33A is particularly highly expressed throughout all cell layers of the cortex and hippocampus (Cheng *et al.*, 2006). In neurons, the protein preferentially accumulates in growing axons and is found both in Golgi membranes and in synaptophysin-positive vesicles that are transported along the growing axons (Nakazawa *et al.*, 2012). RAB33A downregulation inhibits the anterograde axonal transport of these vesicles while its overexpression results in their excessive accumulation and the formation of supernumerary axons (Nakazawa *et al.*, 2012), suggesting that RAB33A mediates axonogenesis and anterograde axonal transport of post-Golgi vesicles. Although RAB33B shares strong sequence homology with RAB33A (especially in the effector domain, which is

perfectly conserved), functional studies have assigned a role for RAB33B in the regulation of the retrograde transport of vesicles between the Golgi and the ER (Starr *et al.*, 2010). Interestingly, RAB33B and RAB6A cooperate in regulating Golgi-to-ER trafficking and are thought to act through a common RAB cascade in which the active form RAB33B recruits the GEFs necessary to activate RAB6A (Pusapati *et al.*, 2012). In addition, RAB33B plays a role in autophagy by modulating autophagosome formation through an interaction with Atg16L (Ao *et al.*, 2014).

Like RAB33B, RAB39B is a neuron-specific protein that is localized to the Golgi apparatus (Giannandrea *et al.*, 2010). Interestingly, both its downregulation and overexpression in mouse primary hippocampal neurons significantly affect neuronal branching, the density of presynaptic boutons and subsequent synapse formation (Giannandrea *et al.*, 2010; Vanmarsenille *et al.*, 2014; Wilson *et al.*, 2014). This suggests that the tightly tuned expression of RAB39B is required for proper neuronal maturation and further illustrates the direct link between Golgi-associated RABs and the specification and maintenance of post-mitotic neurons.

3. Syndromes with postnatal onset microcephaly (POM) and causative genes

3.1 Postnatal-onset microcephaly

Postnatal-onset microcephaly (POM) reflects a failure of the brain to achieve its normal growth after birth, implicating mechanisms occurring during infancy or childhood and involved in its maturation rather than those involved in its formation. At birth, the human brain is only at around 60% of its adult size. The processes critical to ensure the establishment of a functional neuronal network largely take place postnatally, throughout childhood, adolescence and even into adulthood (**Figure 2**): while most neurons are produced and migrate during corticogenesis (i.e. during the first two trimesters), synaptogenesis, which starts at mid-gestation, massively increases during the first two years of life and continues throughout childhood. Synaptic pruning, the process by which extra synapses are selectively eliminated, starts during the third

trimester, increases in childhood and lasts until adulthood. Similarly, the myelination process, by which oligodendrocytes enwrap axons to generate a myelin sheath, starts during the third trimester of gestation and peaks around two to three years of age, but persists throughout childhood and adolescence and continues into adulthood (Back *et al.*, 2002; Bercury and Macklin, 2015). In line with this prolonged role of glial cells, gliogenesis, though very active around 32-40 weeks of gestation, largely continues after birth, especially during the first two years of life (Stiles and Jernigan, 2010). POM, which likely results from the impairment of one or several of these maturation processes, thus consistently becomes apparent during the first two years of age (**Figure 2**). In most cases, POM is associated with cognitive impairments of variable severity and outcome, collectively referred as to intellectual disability. Regardless of the pathophysiological mechanism involved, as for primary microcephaly, POM has multiple etiologies that may be genetic or environmental. A good classification has been proposed in the review by Ashwal and colleagues (Ashwal *et al.*, 2009), and distinguishes, among the genetic causes of POM, inborn errors of metabolism from the syndromic forms of POM.

The most famous syndrome consistently associated with POM is undoubtedly Rett syndrome (RTT). Among the many neurological and behavioral features that characterize the complex clinical spectrum of this neurodevelopmental disorder, typical criteria include a normal period of development followed by a deceleration of head growth in the first two years of life, associated with cognitive deterioration and seizures (Liyanage and Rastegar, 2014; Pohodich and Zoghbi, 2015). Neuropathological examinations reveal reduced cortical thickness associated with smaller and more closely packed neuronal cell bodies, but no active neurodegeneration (Bauman *et al.*, 1995). Local myelin abnormalities and abnormal membrane-bound inclusions in oligodendrocytes have also been reported in several RTT cases, suggesting an involvement of white matter defects in the microcephaly associated with RTT patients (Lekman *et al.*, 1991; Papadimitriou *et al.*, 1988). *MeCP2*, the major RTT gene, encodes a methyl-CpG binding protein that binds methylated DNA. Initially thought to act as a

transcriptional repressor to modulate the transcription of target neuronal genes (Ausio *et al.*, 2014), MeCP2 has turned out to be a multifunctional protein with many interactors and several roles in the CNS. It is expressed in microglia, astrocytes and oligodendrocytes in addition to neurons (Cronk *et al.*, 2016), and is located in cellular compartments other than the nucleus, such as the cytosol (Miyake and Nagai, 2007), the post-synaptic compartments of neurons (Aber *et al.*, 2003) and even the centrosome (Bergo *et al.*, 2015). In line with this, a role for MeCP2 in microtubule stability and vesicular transport has been suggested recently (Delepine *et al.*, 2013; Roux *et al.*, 2012).

3.2 Golgi-associated proteins implicated in POM

Vesicular routing within the cell is highly dependent on microtubules, and the Golgi apparatus is central to this process as it not only drives translational modifications of freshly synthesized proteins and lipids but also orchestrates the complex process that allows them to be packed into specific transport vesicles and routed to their final destinations (Boncompain and Perez, 2013b). As detailed in the introduction, this is even more relevant in the case of neurons and oligodendrocytes. In line with the involvement of the secretory pathway in brain maturation, an increasing number of genes that have been recently associated with syndromic or isolated POM appear to encode Golgi proteins involved in the regulation of the Golgi-mediated traffic machinery, including vesicle targeting and membrane recycling (**Table II**).

3.2.1 *Cohen syndrome and COH1/VPS13B*

Cohen syndrome (COH, MIM 216550) is an autosomal recessive disorder characterized by motor delays, retinal dystrophy appearing by mid-childhood, progressive severe myopia, hypotonia, joint hypermobility and progressive POM associated with intellectual disability (Wang *et al.*, 1993). Brain MRI reveals a relatively large corpus callosum in some patients, associated with markedly smaller sagittal diameters of the brain stem (Kivitie-Kallio *et al.*,

1998). While the neurological signs are most prominent, additional features such as short stature, small hands and feet or childhood-onset obesity have also been reported in some patients but are not constant (Falk *et al.*, 2004). COH1, the only gene associated with Cohen syndrome so far, encodes VPS13B, a large peripheral membrane protein that displays regions homologous to yeast vacuolar protein sorting-associated protein 13 (Vps13p), and is active in the Golgi (Seifert *et al.*, 2011). VPS13B has recently been found to colocalize and interact physically with the active form of RAB6 (Seifert *et al.*, 2015). Depletion experiments using RNAi against RAB6 show that it is required for VPS13B recruitment to Golgi membranes. Conversely, the downregulation of VPS13B or a blockade of its recruitment to the Golgi apparatus results in the fragmentation of Golgi ribbons and a simultaneous inhibition of neurite outgrowth in hippocampal neurons (Seifert *et al.*, 2011; Seifert *et al.*, 2015). Thus, the gene responsible for Cohen syndrome likely encodes an effector protein of RAB6 with a specific role in the dynamics and function of the Golgi apparatus in particular during neuronal maturation (**Figure 1B**).

3.2.2 *PCCA2 syndrome and VPS53*

Progressive Cerebello-Cerebral Atrophy type 2, also named Ponto-Cerebellar Hypoplasia type 2E (PCCA2/PCH2E, MIM 615851) is an autosomal recessive neurodegenerative disorder characterized by normal development during the first three to five months of life, followed by motor delays, progressive POM, progressive spasticity leading to contracture and epileptic seizures prior to two years of age (Ben-Zeev *et al.*, 2003). Patients have a normal head circumference at birth and undergo progressive growth deceleration, resulting in microcephaly during the first year of life. Brain MRI reveals a gradual decrease in cerebral white matter associated with delayed myelination and thinning of the corpus callosum (Ben-Zeev *et al.*, 2003). The responsible gene, mapped and identified in 2014, encodes VPS53, a vacuolar protein-sorting protein that participates in the transport and recycling of endosome-

derived transport vesicles (Feinstein *et al.*, 2014). VPS53 is part of two large multisubunit complexes named Golgi-associated retrograde protein (GARP) and Endosome-associated recycling protein (EARP). Both GARP and EARP ensure the proper tethering between endosomes and their acceptor compartment. GARP is a peripheral complex associated with the TGN and is involved in tethering retrograde transport carriers from endosomes to the TGN (Bonifacino and Hierro, 2011). EARP, characterized more recently, is localized to recycling endosomes and promotes their fast recycling back to the plasma membrane (Schindler *et al.*, 2015). Both complexes cooperate with SNAREs for subsequent membrane fusion. RAB proteins play an essential role during these tethering-fusion steps as they recruit the required tethering factors. In line with this role, GARP has been found to interact with RAB6A at the TGN (Liewen *et al.*, 2005) and EARP associates with RAB4-containing vesicles (Schindler *et al.*, 2015). Thus, the gene responsible for PCCA2 syndrome encodes a subunit of tethering complex proteins that specifically interact with RAB GTPases during endosomal transport in between the TGN and the plasma membrane (**Figure 1B**).

3.2.3 *Warburg-Micro syndrome and RAB3GAP1/2, RAB18 and TBC1D20*

Warburg-Micro syndrome (WARBM1, MIM 600118) is an autosomal recessive disorder characterized by neurodevelopmental defects, severe visual impairment and hypogonadism (Warburg *et al.*, 1993). Neurodevelopmental features generally include POM with profound intellectual disability and progressive limb spasticity associated with progressive peripheral axonal neuropathy (Bem *et al.*, 2011). Brain MRI shows predominantly frontal polymicrogyria bilaterally, and hypoplasia of the corpus callosum and cerebellar vermis (Handley *et al.*, 2013; Liegel *et al.*, 2013). Loss-of-function mutations in four distinct genes, RAB3GAP1, RAB3GAP2, RAB18 and TBC1D20, have been implicated in WARBM1 in recent years (Aligianis *et al.*, 2005; Borck *et al.*, 2011; Liegel *et al.*, 2013). RAB18 has been linked to several distinct membrane-bound organelles such as endosomes (Lutcke *et al.*, 1994),

peroxisomes (Gronemeyer *et al.*, 2013), secretory granules (Vazquez-Martinez *et al.*, 2007) and the ER, and to lipid droplet formation (Martin *et al.*, 2005; Ozeki *et al.*, 2005), depending upon circumstances and cell types. More recent studies have confirmed its localization in the ER and the *cis*-Golgi compartment (Dejgaard *et al.*, 2008). The RAB3GAP complex, initially identified as a GTPase activating protein (GAP) specific to the RAB3 subfamily of small G proteins (Fukui *et al.*, 1997; Nagano *et al.*, 1998), is also a GEF (guanine nucleotide exchange factor) of RAB18 (Gerondopoulos *et al.*, 2014). TBC1D20, an ER-localized GAP that promotes the hydrolysis of RAB1 GTP (Haas *et al.*, 2007; Sklan *et al.*, 2007), is thought to act on RAB18 as well (Handley *et al.*, 2015). Thus, RAB3GAP1, RAB3GAP2 and TBC1D20 all play a role in the regulation of the RAB18 activity, directly linking WARBM1 to RAB18 deficiency or dysregulation. RAB3GAP and TBC1D20 also regulate the ER localization of RAB18, an essential step to support the function of RAB18 in the control of ER structural integrity and retrograde membrane recycling from the Golgi apparatus to the ER (Gerondopoulos *et al.*, 2014; Handley *et al.*, 2015). Thus, the genes involved in WARBM1 all pinpoint a specific RAB-dependent pathway directly associated with ER-Golgi trafficking (**Figure 1B**).

3.2.4 *Autosomal recessive mental retardation 13 (MRT13) and TRAPPC9*

Loss-of-function mutations in the *TRAPPC9* gene were originally identified by autozygosity mapping in four families with a nonsyndromic autosomal recessive intellectual disability (MRT13, MIM 613192) (Mir *et al.*, 2009; Mochida *et al.*, 2009; Philippe *et al.*, 2009). Since then, 3 additional cases have been reported. Although initially referred to as nonsyndromic, the phenotype that is starting to emerge appears to be quite distinctive, including moderate to severe POM, a peculiar facial appearance, obesity and hypotonia. Reported brain anomalies consistently include a reduced volume of the cerebral white matter with a hypersignal on FLAIR sequences, and a marked thinning of the corpus callosum (Abou Jamra *et al.*, 2011; Kakar *et al.*, 2012; Marangi *et al.*, 2013). TRAPPC9 is one of the subunits

of the Trafficking Protein Particle (TRAPP) complex, which mediates the tethering of COPII-coated ER-derived vesicles to allow their fusion with *cis*-Golgi membranes (Barrowman *et al.*, 2010). The TRAPP complex acts through the recruitment and activation of the GTPase RAB1, which in turn recruits specific *cis*-Golgi effectors such as p115 and GM130, allowing the tethering of the vesicles to Golgi membranes (Barnekow *et al.*, 2009). During this anterograde ER-to-Golgi transport, the TRAPP complex is dynamically associated with the microtubules through a physical interaction with $p150^{Glued}$, a subunit of dynactin. A recent study has proposed that TRAPPC9 in particular mediates the interaction between $p150^{Glued}$ and COPII-coated vesicles until they reach their target membrane (Zong *et al.*, 2012), evoking an additional paradigm in which RAB-associated ER-Golgi trafficking linked to POM and white matter defects (**Figure 1B**).

3.2.5 *A neuromuscular syndrome with microcephaly and GOLGA2/GM130*

A homozygous frame-shift deletion in the *GOLGA2* gene that results in a loss of gene function has recently been identified in an individual with a neuromuscular phenotype characterized by developmental delays, seizures, progressive microcephaly starting at 4 months of age, hypotonia and muscular dystrophy (Shamseldin *et al.*, 2016). Here also, brain MRI has revealed delayed myelination and a thinning of the corpus callosum, but with no other specific loss of cerebral volume. *GOLGA2* encodes the Golgi matrix protein GM130, which is a peripheral membrane protein located on the *cis*-side of the Golgi apparatus and involved in both the assembly/maintenance of Golgi structure and the regulation of the secretory pathway (Nakamura, 2010). As mentioned above in the case of TRAPPC9, GM130 participates in membrane-tethering events at the Golgi complex through dynamic interactions with RAB1 and other tethering proteins such as p115, to ensure efficient anterograde cargo delivery to the *cis*-Golgi compartment. Moreover, GM130 binds to other RAB proteins involved in membrane traffic regulation at the ER/Golgi interface, such as RAB2 and RAB33B (Short *et al.*, 2001;

Valsdottir *et al.*, 2001). Thus, GOLGA2/GM130 deficiency appears to be yet another situation highlighting the link between Golgi-associated RABs, POM and white matter defects (**Figure 1B**).

3.2.6 *Dyggve-Melchior-Clausen syndrome and DYMECLIN*

Dyggve-Melchior-Clausen syndrome (DMC, MIM #223800) is an autosomal recessive skeletal dysplasia associated with POM and intellectual disability, and caused by loss-of-function mutations in the *DYM* gene encoding DYMECLIN, a Golgi protein involved in intracellular trafficking (Dimitrov *et al.*, 2009; Osipovich *et al.*, 2008; Paupe *et al.*, 2004). Brain MRI in DMC patients with a truncating mutation in *DYM* reveals a marked thinning of the corpus callosum and brain stem (Dupuis *et al.*, 2015). In line with this finding, recent data from our group show a significant reduction in white matter volume associated with defects in the way the myelin sheath is wrapped, and a reduced thickness of myelinated axons in *Dym-/-* mutant mice (Dupuis *et al.*, 2015). Interestingly, Dym-deficient neurons display a fragmented Golgi apparatus and impaired ER-to-Golgi trafficking (Dupuis *et al.*, 2015). However, an impairment of the retrograde transport of vesicles from the Golgi to the ER has also been suggested in *Dym-/-* mouse embryonic fibroblasts (Osipovich *et al.*, 2008). Although DYMECLIN function is still elusive at the molecular level, several lines of evidence suggest that it has a tethering role during vesicle trafficking between the ER and the Golgi: (i) DYMECLIN localizes to both the cytosol and the periphery of *cis*-Golgi membranes, and permanently shuttles between these two compartments (Dimitrov *et al.*, 2009), (ii) DYMECLIN colocalizes and directly interacts with GIANTIN (Dimitrov *et al.*, 2009; Osipovich *et al.*, 2008), a giant Golgi-resident protein of the golgin family that forms complexes with RAB1 or RAB6 to tether Golgi membranes with membrane structures derived from the ER (anterograde pathway) or returning to the ER (retrograde pathway), respectively (Goud and Gleeson, 2010; Koreishi *et al.*, 2013; Rosing *et al.*, 2007) (**Figure 1B**).

Interestingly, Smith McCort dysplasia, a clinical variant of DMC syndrome with identical skeletal defects but normal intelligence and no microcephaly, has been found to result either from specific missense mutations in *DYM* that could result in some residual activity of the protein (SMC1, MIM #607326) (Cohn *et al.*, 2003; Dimitrov *et al.*, 2009) or from loss-of-function mutations in the small GTPase RAB33B (SMC2, MIM #615222) (Alshammari *et al.*, 2012; Dupuis *et al.*, 2013). Given that the main functional domains of RAB33A and RAB33B proteins are perfectly conserved (Zheng *et al.*, 1998), it is tempting to speculate that the cerebral phenotype in SMC is rescued by the partial activity of DYMECLIN (SMC1) or a complementation of RAB33B deficiency by RAB33A in the brain (SMC2). Interestingly, both RAB33A and RAB33B are present in the Golgi complex (Cheng *et al.*, 2006; Zheng *et al.*, 1998) and are involved in the regulation of vesicular transport: while RAB33B functions in concert with RAB6 to coordinate bidirectional intra-Golgi and retrograde Golgi-to-ER transport (Starr *et al.*, 2010), RAB33A has been shown to mediate the anterograde transport of post-Golgi vesicles in growing hippocampal axons (Nakazawa *et al.*, 2012). Although the precise link between DYM, RAB33A/B and RAB6 is yet to be understood, these factors likely function in the regulation of common Golgi-driven secretory pathways.

3.2.7 *Congenital disorders of glycosylation and the COG complex*

Congenital Disorders of Glycosylation (CDG) represent a huge and still growing family of multisystemic autosomal recessive pathologies involving dysfunctions in the processing of N- and O-linked glycans, with most of the genes identified so far encoding glycosylation enzymes (Freeze and Ng, 2011). However, one subgroup of these diseases involves the Conserved Oligomeric Golgi (COG) complex, a hetero-octameric protein complex, which, as its name suggests, is localized to the *cis* and medial Golgi as well as surrounding vesicles (Climer *et al.*, 2015). The COG complex is thought to act as a tethering factor, in particular during intra-Golgi and retrograde Golgi-to-ER trafficking, where it mediates the recycling of

Golgi glycosyltransferases (Shestakova *et al.*, 2006). Loss-of-function mutations in seven of the eight COG subunits have been associated with CDG, possibly due to the accumulation of COG complex-dependent vesicles, likely resulting in the segregation of Golgi glycosylation enzymes from their target proteins (Climer *et al.*, 2015). Mutations affecting the COG complex thus result in multiple protein glycosylation deficiencies. Among the many neurological manifestations described in COG-associated CDG, POM has been reported in patients carrying mutations in COG1, COG2, COG7 and COG8 (Foulquier *et al.*, 2007; Foulquier *et al.*, 2006; Kodera *et al.*, 2015; Morava *et al.*, 2007). In addition, hypoplasia of the corpus callosum has been observed on brain MRI in four patients (Kodera *et al.*, 2015; Morava *et al.*, 2007) and brainstem atrophy has been reported in one case (Foulquier *et al.*, 2007). Interestingly, the COG complex has been shown to interact with molecules at all levels of Golgi organization and trafficking, including several Golgi-associated SNAREs (Laufman *et al.*, 2013a; Laufman *et al.*, 2011, 2013b; Laufman *et al.*, 2009; Shestakova *et al.*, 2007), golgins such as p115, GM130, GIANTIN and GOLGIN-84 (Miller *et al.*, 2013; Shestakova *et al.*, 2007; Sohda *et al.*, 2010; Sohda *et al.*, 2007), vesicular coatomers such as COPI, and molecular motors (Kristensen *et al.*, 2012; Miller *et al.*, 2013) as well as a number of Golgi-associated RABs. Among the latter are RAB1A/B, RAB2A, RAB6A/B, RAB10, RAB14, RAB30, RAB36, RAB39 and RAB41 (reviewed in (Willett *et al.*, 2013)), again pointing to the relationship between defects in these functionally important Golgi-associated proteins on the one hand, and POM and white matter defects on the other (**Figure 1B**).

4. Possible mechanisms underlying postnatal microcephaly

A consistent finding in all the disorders described above is the presence of white matter defects, and in particular of abnormalities of the corpus callosum, which, thanks to its relatively high visibility in live imaging modalities as well as conventional histology, could rightly be considered a window into the diseased brain. Although white matter, which is made up of millions of axon bundles that interconnect neurons throughout the brain into functional circuits, accounts for half the volume of the human brain, its role in brain maturation and homeostasis is still far less studied than that of the cortex. Yet, it is essential for impulse conduction, and is thought to participate actively in higher functions such as learning, reasoning (in particular mathematical thinking (Matejko and Ansari, 2015)), and memory (Fields, 2010). Consistent with this broad involvement, axonal transport defects are now being described in an increasing number of degenerative disorders such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease and hereditary spastic paraplegia etc. (Duncan and Goldstein, 2006; Neefjes and van der Kant, 2014). The fragmentation and dispersal of the Golgi apparatus has been documented as an early event in these degenerative processes (Gonatas *et al.*, 2006; Haase and Rabouille, 2015; Joshi *et al.*, 2015), and the Golgi, in addition to being a sensor of stress signals in cell death pathways (Machamer, 2015; Nakagomi *et al.*, 2008), may be actively involved in degeneration (Rabouille and Haase, 2015).

However, defective Golgi trafficking is not only an important issue in neurodegenerative conditions but during development, including in predominantly postnatal processes such as the maturation of white matter, as indicated by its involvement in POM highlighted in the present review. The demand for secretory traffic increases exponentially as axons elongate, dendrites multiply and myelination increases. If even a single link in the supply chain is deficient, whether in neurons or the oligodendrocytes that myelinate them, the Golgi apparatus likely detects this stress, which, beyond a certain threshold, becomes detrimental and affects cell

maturation and maintenance. Additionally, in many cases of POM, as detailed above, the deficient link appears to be none other than a member of the Golgi-mediated secretory traffic machinery. The implication of several Golgi-associated RABs in the pathophysiology of POM highlights the central role of the Golgi apparatus in dynamically receiving and generating specific membrane vesicles both in large quantities and in a highly controlled manner. Thus, one possible mechanism responsible for the development of POM could be an insufficient supply of synaptic and/or oligodendrocytic cargos due to a defective secretory pathway in these highly demanding cells (Dupuis *et al.*, 2015). Such a defect may be due to ineffective transport, alteration in cargo maturation (e.g. glycosylation, proteolysis) or problems in routing to the proper target compartment. Defective secretory trafficking combined with hypomyelination likely leads to an impairment of synaptic transmission, contributing to the intellectual disability observed in POM patients and perhaps further weakening diseased neurons. Thus, while POM or acquired microcephaly is not traditionally considered a disorder on its own but rather as a clinical feature present in various genetic syndromes, and several syndromes featuring POM are associated with genes and functions that do not directly involve membrane trafficking (Seltzer and Paciorkowski, 2014), we believe that there exists a distinct subset of POM with similar pathophysiological mechanisms and clinical manifestations. We propose that this distinct and coherent ensemble of causes and effects – defects in Golgi-associated RABs or their partners, altered trafficking of molecules, vesicles and membrane components essential for neuronal and oligodendrocytic activity, the resulting defective myelination and synaptic function and finally, microcephaly with a postnatal onset independent of neural progenitor proliferation or migration – be named "Golgipathic microcephalies".

The impairment of autophagic pathways is also likely implicated in the pathophysiology of POM and may be related to defects in the conventional secretory pathway. Among the autophagy-related molecules involved in POM, the tethering complex GARP (of which VPS53, involved in PCCA2, is a subunit) is recruited at the phagophore membrane during

autophagosome assembly (Yang and Rosenwald, 2016). TBC1D20, one of the genes associated with Warburg-Micro syndrome, plays an essential role in the maturation of autophagosomes via its RAB1BGAP function (Sidjanin *et al.*, 2016). RAB33A and B are known to modulate autophagosome formation through their interaction with ATG16L (Itoh *et al.*, 2008). The vesicle-tethering golgin GM130 has also been shown to participate in the regulation of autophagy through dynamic interactions with GABARAP and WAC proteins (Joachim *et al.*, 2015). It is also likely that some syndromes involving defective autophagy do indeed include POM among their symptoms, but that this link has been missed among the multitude of other symptoms involved, or ignored because of a lack of understanding regarding the underlying cause. For instance, a form of hereditary spastic paraplegia linked to mutations in TECPR2, which regulates COPII-dependent vesicle formation (Stadel *et al.*, 2015), has recently been shown to include progressive microcephaly among its symptoms (Heimer *et al.*, 2016; Oz-Levi *et al.*, 2012), although it is not yet known whether this is due to neurodevelopmental or neurodegenerative processes. As mentioned previously, several other ER/Golgi-associated RAB proteins such as RAB1, RAB11 and RAB24, are also involved in the regulation of autophagy, further highlighting the crosstalk, if not the overlap, between Golgi membrane trafficking and autophagy pathways (Jain and Ganesh, 2016) (**Table I**).

The clinical manifestations of "Golgipathies" may not be restricted to the white matter or myelinated neurons predominantly affected in POM. The Golgi apparatus obviously plays a crucial role in numerous cell types, a fact supported by the diversity of other symptoms displayed by patients with "Golgipathies": stunted growth, neuromuscular dysfunctions, metabolic disorders, pubertal anomalies etc. It is unclear at present in what cells and to what extent Golgi trafficking deficits in other organs and tissues contributes to the phenotype in these syndromes. Besides, with regard to disorders of the autophagic pathway and the putative overlap between the molecular machinery involved in this pathway and that traditionally associated with trafficking, other symptoms that have been overlooked until now may also turn

out to form part of the clinical spectrum. In addition, although neurodegeneration has not been shown to be involved in the types of POM described in the present review, it cannot be ruled out, as the long-term evolution of the cases reported so far is unknown. However, it is worth noting that retinal degeneration has been documented in Cohen syndrome (North *et al.*, 1995), and sensory axon degeneration associated with a deletion of RAB18 has recently been described in a mouse model of Warburg-Micro syndrome (Cheng *et al.*, 2015). Future investigations into POM-related syndromes where the responsible gene has not been identified should therefore be carried out in light of the notion of Golgi trafficking defects as a possible etiology.

5. Conclusion

The newly identified defects in certain Golgi-associated proteins, including RABs and their interactors, that we have highlighted in the present review and propose to name "Golgipathic microcephalies" or "Golgipathies", and more broadly, the notion that the primary deregulation of the trafficking machinery is itself a mechanism leading to POM, is clearly an emerging research area that it would be important to investigate in coming years. Future studies in this field will surely improve our understanding of the molecular mechanisms linking Golgi function and the maturation of white matter, in addition to extending the predicted and observed phenotype of patients with these disorders and creating new avenues to optimize cognitive outcome by reversing part of the maturation defects.

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Legends to Figures

Figure 1.

Golgi-associated postnatal microcephaly-causing factors and their link with RAB proteins in anterograde and retrograde neuronal trafficking

A. Schematic representation of the somatic Golgi apparatus, dendritic Golgi outposts and differential organization of microtubules in axons and dendrites. B. Subcellular localization of the proteins whose encoding genes have been associated with postnatal-onset microcephaly, and their known link with Golgi-associated RAB GTPases.

EE = Early Endosome. ER = Endoplasmic Reticulum. ERGIC = Endoplasmic Reticulum-Golgi Intermediate Compartment. GA = Golgi Apparatus. GO = Golgi Outposts. GS = Golgi Satellites. L/A = Lysosome/Autophagosome. LE = Late Endosome. MT = MicroTubules. Nu = Nucleus. RE = Recycling Endosome. TGN = Trans Golgi Network.

Figure 2.

Time-course of the main neurodevelopmental steps in human and correspondence with the Occipito-Frontal Circumference progression

Schematic representation of the main neurodevelopmental mechanisms contributing to brain growth illustrating that gliogenesis, synaptogenesis, myelination and synaptic pruning mainly occur during childhood (although initiated before birth) and significantly contribute to postnatal brain growth (black curve). The red and blue curves illustrate the progression of occipito-frontal circumference (OFC) in patients affected with postnatal microcephaly (POM) and primary microcephaly (PM) respectively.

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TABLE I. GA/TGN-associated RAB GTPases and their associated function(s).

RAB GTPase Sub-family	Subcellular location	Known intracellular function	References
RAB1	Cis-Golgi - ER/Intermediate compartment	ER-Golgi trafficking, Cell signaling, Autophagy	(Ao *et al.*, 2014; Yang and Rosenwald, 2016)
RAB2	Cis-Golgi, Intermediate compartment, vesicles	Regulation of GA morphology, Axonal transport	(Aizawa and Fukuda, 2015; White *et al.*, 2015)
RAB3	Golgi, TGN, secretory vesicles	Exocytosis	(Kogel *et al.*, 2013; Nishimura *et al.*, 2008)
RAB6	Golgi, TGN, peroxisomes	Golgi vesicle biogenesis, Anterograde & retrograde vesicle transport from the trans-Golgi/TGN to the plasma membrane or ER	(Heffernan and Simpson, 2014; Majeed *et al.*, 2014)
RAB7	TGN, late endosomes	Transport to late endocytic compartments, Cell signaling, Autophagy	(Ao *et al.*, 2014; Guerra and Bucci, 2016)
RAB8	TGN, vesicles, tubular structures	Membrane trafficking from the TGN, Exocytosis, Membrane recycling, Autophagy	(Ao *et al.*, 2014; Peranen, 2011)
RAB9	Golgi, TGN, late endosomes	Endosome-to-TGN transport, Transport within the endolysosomal system, Golgi targeting of glycosphingolipids, Autophagy	(Ao *et al.*, 2014; Kucera *et al.*, 2016)
RAB10	Golgi, ER tubular intermediates, peroxisomes	Membrane trafficking from the Golgi/ER, the TGN and recycling endosomes, Dendritic transport	(Homma and Fukuda, 2016; Zou *et al.*, 2015)
RAB11	Golgi, ER tubular intermediates, TGN, recycling endosomes	Recycling endosomes, Exocytosis, Autophagy	(Ao *et al.*, 2014; Takahashi *et al.*, 2012; Wilson *et al.*, 2016)
RAB12	Golgi, early endosomes, toxin-induced membrane invaginations	Transport within the endolysosomal system, Retrograde transport to TGN, Autophagy	(Matsui and Fukuda, 2011, 2013; Rydell *et al.*, 2014)
RAB13	TGN, endosomes, plasma membrane	Recycling endosomes, Membrane trafficking from the TGN	(Kobayashi *et al.*, 2014; Nokes *et al.*, 2008)
RAB14	Golgi, TGN, early endosomes, peroxisomes	membrane trafficking between the Golgi complex and endosomes, Autophagy	(Junutula *et al.*, 2004; Okai *et al.*, 2015)
RAB15	TGN, early and recycling endosomes	Early endocytic trafficking	(Zuk and Elferink, 2000)
RAB18	Cis-Golgi - ER, *endosomes*, *peroxisomes*, *secretory granules*, *lipid droplets*	ER structure, ER-Golgi trafficking, secretory granule transport	(Dejgaard *et al.*, 2008; Gerondopoulos *et al.*, 2014; Vazquez-Martinez and Malagon, 2011)
RAB19	Golgi, vesicles	Axonal transport	(Sinka *et al.*, 2008; White *et al.*, 2015)
RAB21	TGN, endosomes	Neurite Outgrowth Early endocytic pathway, Autophagy	(Burgo *et al.*, 2009; Jean *et al.*, 2015; Simpson *et al.*, 2004)
RAB22	Trans-Golgi, TGN, endosomes	Neurite Outgrowth Early endocytic pathway	(Dutta and Donaldson, 2015; Rodriguez-Gabin *et al.*, 2001; Wang *et al.*, 2011)

RAB24	ER, Cis-Golgi, late endosomes, Autophagosomes, midbody	endosome-lysosome degradative pathway, Cytokinesis, Autophagy	(Amaya *et al.*, 2016; Militello *et al.*, 2013; Olkkonen *et al.*, 1993; Yla-Anttila *et al.*, 2015)
RAB26	Golgi, synaptic vesicles, Lysosomes	Golgi-to-cell surface traffic, lysosome traffic, Autophagy	(Binotti *et al.*, 2015; Jin and Mills, 2014; Li *et al.*, 2012)
RAB27	TGN, secretory granules	secretory granule transport and exocytosis	(Fukuda, 2013)
RAB29	Golgi, TGN, recycling endosomes	Integrity of the TGN, Recycling from late endosomes to the TGN	(Onnis *et al.*, 2015; Wang *et al.*, 2014)
RAB30	Golgi	Integrity of the Golgi apparatus, Autophagy	(Kelly *et al.*, 2012; Oda *et al.*, 2016)
RAB33	Golgi, synaptic vesicles	axonal transport (RAB33A), Retrograde Golgi-to-ER transport (RAB33B), Autophagy	(Ao *et al.*, 2014; Itoh *et al.*, 2008)
RAB34	Golgi, Lysosomes	Intra-Golgi anterograde transport, lysosomes trafficking , Autophagy	(Goldenberg *et al.*, 2007; Kasmapour *et al.*, 2012; Starling *et al.*, 2016)
RAB35	TGN, endosomes, plasma membrane	Endocytic recycling, Neurite Outgrowth, Exosome release, Cytokinesis & cell polarity	(Klinkert and Echard, 2016)
RAB36	Golgi, Lysosomes, recycling endosomes	Endosomes and lysosomes trafficking, Neurite Outgrowth	(Chen *et al.*, 2010; Kobayashi *et al.*, 2014)
RAB38	ER, Golgi, TGN, post-Golgi vesicles	biogenesis of lysosomes/melanosomes	(Bultema and Di Pietro, 2013; Osanai *et al.*, 2005; Wasmeier *et al.*, 2006)
RAB39	Golgi	Neurite morphology, Autophagy	(Chen *et al.*, 2003; Corbier and Sellier, 2016; Mori *et al.*, 2013; Seto *et al.*, 2013)
RAB40	Golgi, plasma membrane, recycling endosomes	Vesicle transport in oligodendrocytes, cell signaling	(Lee *et al.*, 2007; Rodriguez-Gabin *et al.*, 2004)
RAB41	Golgi	Golgi apparatus organization, ER-Golgi trafficking	(Liu *et al.*, 2013)
RAB43	Golgi	Integrity of the Golgi apparatus, anterograde trafficking of cargo through the medial Golgi, Retrograde transport from endosomes to Golgi	(Cox *et al.*, 2016; Dejgaard *et al.*, 2008)

ER=Endoplasmic Reticulum. GA=Golgi apparatus. TGN=Trans Golgi Network.

TABLE II. Genetic disorders associated with POM and Golgi-associated factors.

Disorder	OMIM (disease)	Mode of inheritance	Causing-gene(s)	Gene product	Type(s) of mutation	References (gene identification)
Cohen syndrome	216550	Autosomal Recessive	COH1	VPS13B	nonsense, frameshift, splice site, larger in-frame deletions, missense, complex rearrangement, intragenic heterozygous deletions	(Seifert *et al.*, 2011)
PCCA2 syndrome	615851	Autosomal Recessive	VPS53	VPS53	splice site, missense	(Feinstein *et al.*, 2014)
Warburg-Micro syndrome	600118	Autosomal Recessive	RAB3GAP1	RAB3GAP1	nonsense, frameshift, large insertions/ deletions, missense, splice site	(Aligianis *et al.*, 2005)
			RAB3GAP2	RAB3GAP2	in-frame deletions, missense mutations	(Borck *et al.*, 2011)
			RAB18	RAB18	missense, frameshift, deletions	(Bem *et al.*, 2011)
			TBC1D20	TBC1D20	large deletions, missense, frameshift	(Liegel *et al.*, 2013)
MRT13	613192	Autosomal Recessive	MRT13	TRAPPC9	missense, frameshift	(Mir *et al.*, 2009; Mochida *et al.*, 2009; Philippe *et al.*, 2009)
Neuromuscular syndrome	602580*	Autosomal Recessive	GOLGA2	GM130	missense, frameshift mutations	(Shamseldin *et al.*, 2016)
Dyggve-Melchior-Clausen syndrome	223800	Autosomal Recessive	DYM	DYMECLIN	nonsense, splice site, frameshift, missense, complex duplications	(Cohn *et al.*, 2003; El Ghouzzi *et al.*, 2003)
Congenital disorders of glycosylation (COG subgroup)	611209 *(CDG type 2G)*	Autosomal Recessive	COG1	COG1	nonsense, frameshift	(Foulquier *et al.*, 2006)
	606974*		COG2	COG2	nonsense, missense	(Foulquier *et al.*, 2007)
	608779 *(CDG type 2E)*		COG7	COG7	nonsense, splice site	(Wu *et al.*, 2004)
	611182 *(CDG type 2H)*		COG8	COG8	nonsense	(Foulquier *et al.*, 2007)

* OMIM reference corresponds to the gene instead of the disease

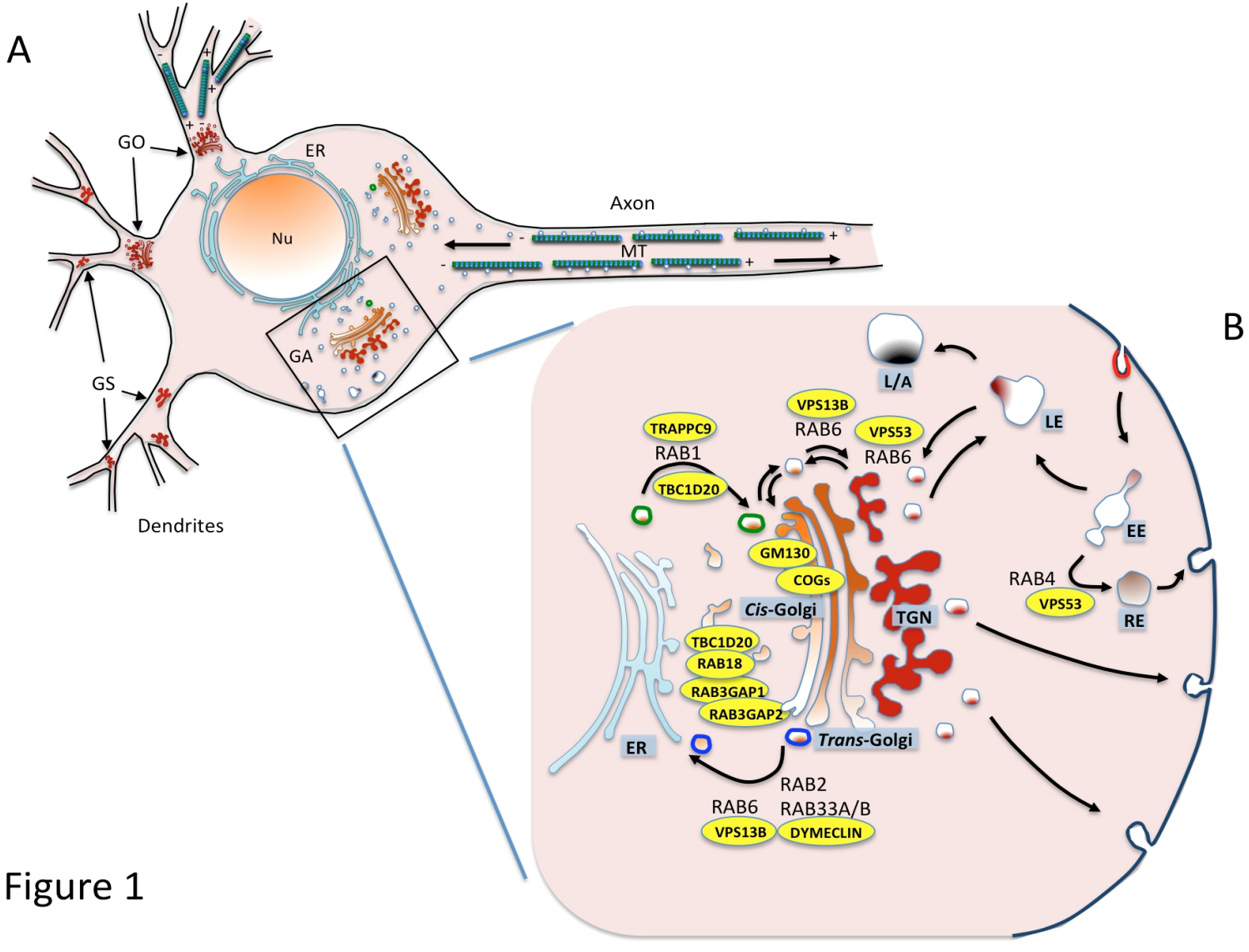
A
GO
ER
Nu
Axon
MT
GA
GS
Dendrites
B
L/A
LE
VPS13B
RAB6
VPS53
RAB6
TRAPPC9
RAB1
TBC1D20
EE
GM130
COGs
RAB4
VPS53
RE
Cis-Golgi
TGN
TBC1D20
RAB18
RAB3GAP1
RAB3GAP2
ER
Trans-Golgi
RAB2
RAB33A/B
RAB6
VPS13B
DYMECLIN

Figure 1

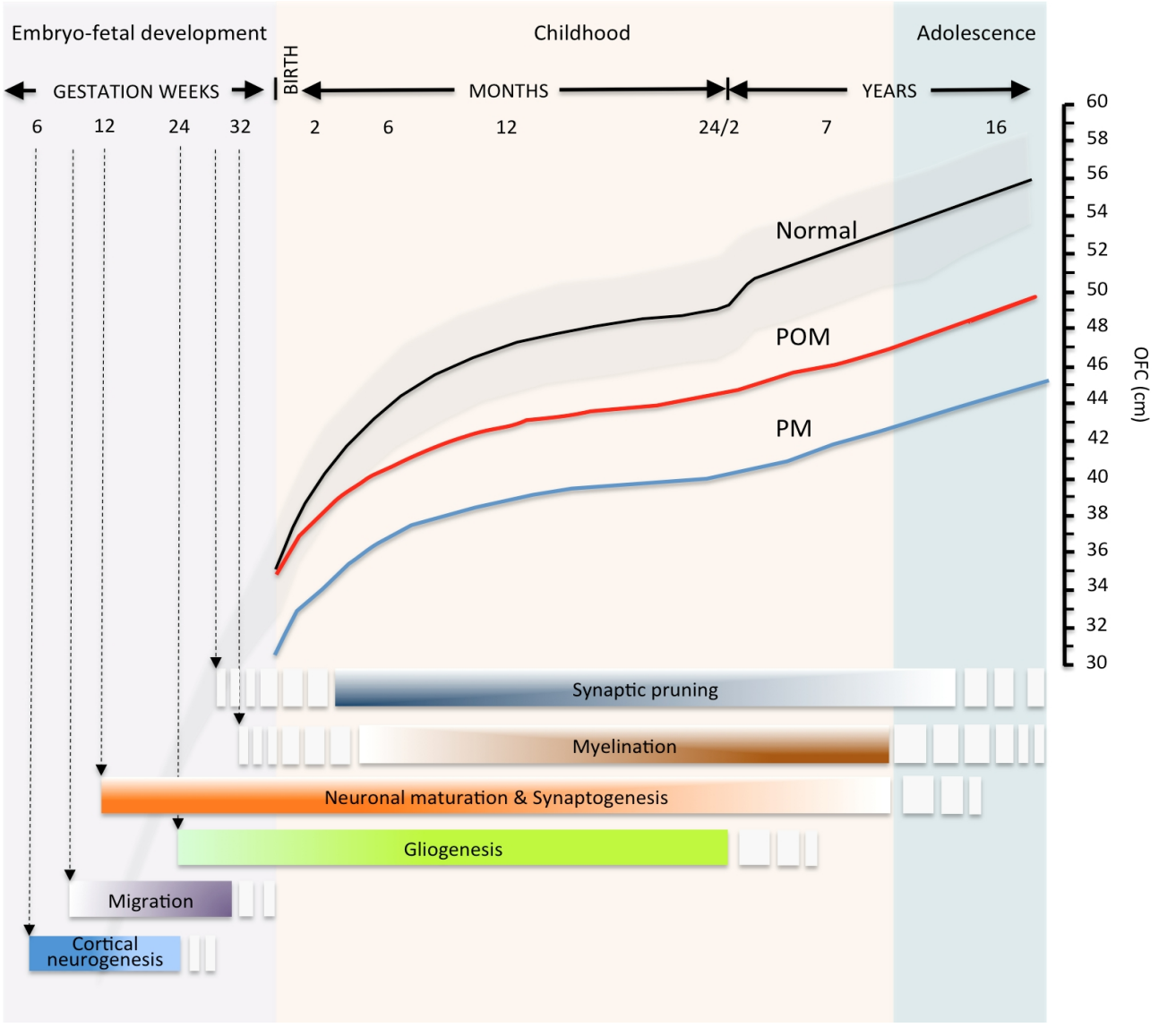
Embryo-fetal development
Childhood
Adolescence
GESTATION WEEKS
BIRTH
MONTHS
YEARS
6
12
24
32
2
6
12
24/2
7
16
Normal
POM
PM
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
OFC (cm)
Synaptic pruning
Myelination
Neuronal maturation & Synaptogenesis
Gliogenesis
Migration
Cortical neurogenesis

Figure 2

Revised Abbreviations List

CDG: Congenital Disorders of Glycosylation

CGN: Cis-Golgi Network

CNS: Central Nervous System

COG: Conserved Oligomeric Golgi

COH: Cohen syndrome

DYM: DYMECLIN

EARP: Endosome-associated recycling protein

ER: Endoplasmic Reticulum

ERGIC: ER-Golgi intermediate Compartment

GAP: GTPase Activating Protein

GARP: Golgi-associated retrograde protein

GEF: Guanine nucleotide Exchange Factor

MBP: Myelin Basic Protein

MCPH: MicroCephaly Primary Hereditary

MRI: Magnetic Resonance Imaging

MTOC: Microtubule Organizing Center

OFC: occipito-frontal circumference

PCCA2: Progressive Cerebello-Cerebral Atrophy type 2

PLP: ProteoLipid Protein

POM: Postnatal-Onset Microcephaly

RTT: Rett syndrome

SNAREs: soluble *N*-ethylmaleimide-sensitive fusion protein attachment proteins

TGN: Trans-Golgi Network

TRAPP: TRAnsport Protein Particle

VPS: Vacuolar Protein Sorting

WARBM: Warburg-Micro syndrome

> An increasing number of inherited disorders that include postnatal-onset microcephaly (POM), white matter defects and intellectual disability are associated with genes encoding Golgi-associated proteins.

> Remarkably, these Golgi-associated proteins link POM and intellectual disability with dysfunctions in RAB-dependent regulatory pathways.

> We propose that this distinct and coherent ensemble of causes and effects be named "Golgipathic microcephalies"/ "Golgipathies".